NHS Low Calorie Diet Pilot Programme
Guidance for GP practices and referrers

30th November 2021 (version 2)

NHS England and NHS Improvement

Background

- The DiRECT trial (2017) tested a low calorie diet (LCD), total diet replacement (TDR) approach in people with Type 2 Diabetes within 6 years of diagnosis to achieve weight loss and remission of diabetes
- On the first day of starting TDR, all glucose-lowering agents and BP-lowering agents were stopped
- At 1 year, 46% of people in the intervention group achieved remission (as defined in the trial), compared to 4% of controls
- Weight loss was strongly associated with achievement of remission. The 2 year data showed that 64% of people with ≥10kg loss at 2 years were in remission, compared to 29% of people with 5-10kg weight loss and 5% of people with <5kg weight loss
- While DiRECT used nurses or dieticians to provide behavioural support, the DROPLET trial (2018) showed that similar weight loss outcomes to DiRECT could be achieved using a trained workforce of non-healthcare professionals to deliver the behavioural support elements of the LCD intervention
- The NHS is running pilots to offer this intervention at scale, in the real world
- People will be supported to lose weight, improve glycaemic parameters and potentially achieve remission of Type 2 Diabetes
- Even if remission is not achieved, people achieving weight loss are likely to benefit from improvements in glycaemia and cardiometabolic risk factors
- Each NHS LCD Programme ICS pilot site has been involved in choosing a delivery model and the commercial process of selecting a provider

Changes due to the COVID-19 pandemic

- Prior to the COVID-19 pandemic, face-to-face one-to-one, face-to-face group and digital one-to-one approaches had been planned, with each LCD ICS pilot site involved in selecting their delivery model
- In the context of the COVID-19 pandemic, all planned delivery approaches for the programme changed to fully remote, given the potential risks relating to viral transmission posed by face-to-face contact
- Alongside remote delivery, self-reported readings of blood glucose, blood pressure (where applicable) and weight will be used for monitoring (with equipment and relevant training supplied by the provider)
- At a later date, once clinically and operationally appropriate, it is anticipated that face-to-face in-person approaches will be implemented in ICSs where these were originally planned
- The manner in which new sites with face-to-face delivery approaches planned will mobilise will be confirmed soon
- It is appreciated that referrals to the NHS LCD Programme may occur through remote consultations in General Practice; according adjustments to eligibility criteria and guidance for referrers have therefore been incorporated

What is low calorie, total diet replacement?

- Total diet replacement (TDR) refers to an approach where usual foods are replaced with a micronutrient-replete formulated diet
- The TDR products usually take the form of shakes or soups, however other product forms are available
- There are a number of commercial entities producing TDR products. The composition of such products is regulated by European legislation
- Generally, a product is consumed at each meal time. Some TDR regimes also include an additional specially-formulated ‘snack’
- When used as intended and no other foods are consumed, the total daily calorie intake on the TDR phase of the NHS LCD Programme is around 800-900 kcals
- Though other approaches such as low calorie diets with ‘real foods’ may be effective for some people, the strongest evidence-base in achieving Type 2 Diabetes remission through non-surgical means is currently with TDR approaches

Aims of the NHS LCD Programme Pilots

- Reduction in weight of Service Users and maintenance of weight loss achieved
- Achievement of remission of Type 2 diabetes / reduced glycaemic parameters
- Reduction in medication usage

- Build the evidence base around the effectiveness of different delivery approaches to the low calorie diet (LCD), total diet replacement (TDR) intervention, such as one-to-one or group sessions, and evidence around impact in different demographic groups

Overview of the Programme

- Referrals to the NHS LCD Programme are from GP practices
- Three phases to the intervention:
    - Total Diet Replacement: 12 weeks
    - Food re-introduction: 4-6 weeks
    - Weight maintenance: Until 12 months
- A rescue protocol (with additional 4 weeks TDR) is available if participant regains ≥ 2kg weight after TDR phase
- There is no direct cost to patients (i.e. they do not pay for the TDR products)

Eligibility criteria – part 1

These are aligned to the evidence-base but have been adapted pragmatically for the real world pilots. Individuals who satisfy all the following eligibility criteria may be referred to the Service:

- Aged 18 to 65 years (inclusive) [the upper age limit is aligned with the evidence-base of DIRECT]
- Diagnosed with Type 2 diabetes within the last 6 years
- BMI ≥ 27kg/m² in people from White ethnic groups (adjusted to ≥ 25kg/m² in people from Black, Asian and other ethnic groups)
    - BMI obtained from self-measured weight is acceptable for referral. If this cannot be obtained, a clinic-measured value within the last 12 months may be used, provided there is no concern that weight may have reduced since last measured such that the individual would not be eligible for the LCD programme at present
- HbA1c measurement taken within the last 12 months, in line with the following:
    - If on diabetes medication (HbA1c result reflects the effect of glucose-lowering medications), HbA1c 43-87 mmol/mol
    - If not on diabetes medication (HbA1c result does not reflect the effect of glucose-lowering medications), HbA1c 48-87 mmol/mol
    - If there is any concern that HbA1c may have changed since last measured, such that repeat testing may indicate that the individual would not be eligible for the LCD programme at present, HbA1c should be rechecked before referral is considered
- Must have attended for monitoring and diabetes review when last offered, including retinal screening, and commit to continue attending annual reviews, even if remission is achieved
- Does not meet any exclusion criteria (see next slide)

Eligibility criteria – part 2

If any of the following apply, the individual is not suitable for referral to the NHS LCD Programme (exclusion criteria):

- Current insulin user
- Pregnant or planning to become pregnant within the next 6 months
- Currently breastfeeding
- Has at least one of the following significant co-morbidities;
    - active cancer
    - heart attack or stroke in last 6 months
    - severe heart failure (defined as New York Heart Association grade 3 or 4)
    - severe renal impairment (most recent eGFR less than 30mls/min/1.73m2)
    - active liver disease (not including NAFLD)
    - active substance use disorder
    - active eating disorder
    - porphyria
    - known proliferative retinopathy that has not been treated.
- Weight loss of greater than 5% body weight in the last 6 months, or is currently on a weight management programme
- Undergone or is awaiting bariatric surgery (unless willing to come off waiting list)
- Health professional assessment that the person is unable to understand or meet the demands or monitoring requirements of the Programme

- ***If not eligible for the LCD Programme, consider whether the individual would benefit from other available weight management support***

Definition of Remission

- The Expert Advisory Group for the NHS LCD Programme agreed the below definition of remission for the purpose of the pilots:
    - Remission has been achieved when **HbA1c < 48mmol/mol (or FPG < 7mmol/l if HbA1c is not clinically suitable) has been maintained for at least 6 months, off all glucose-lowering medications**
- Using this definition, remission therefore requires checking of HbA1c levels (or FPG if HbA1c is not clinically suitable) at least 6 months apart, with no glucose-lowering agents used during this interval.
- It is noted that an international consensus report has recently proposed a similar definition of remission (but with non-diabetic glycaemic levels maintained for at least 3 months rather than at least 6 months). However, for consistency across the NHS LCD Programme, the definition above will continue to be used in the pilots.

Remission of Type 2 Diabetes

- Please make clear that achievement of remission does not mean patients have been cured – specifically use the term ‘remission’
- The mechanism of remission is thought to be the removal of excess fat from the liver and pancreas, allowing these organs to potentially return to normal physiological function in maintaining optimal blood glucose regulation
- Weight gain above an individual’s ‘personal fat threshold for Type 2 Diabetes’ - the body weight at which physiological processes for regulating glucose levels are sufficiently deranged to result in diabetes-range glycaemic parameters – is likely to result in ‘active Type 2 Diabetes’ and the according risks of developing complications
- It is therefore essential that anyone referred to the NHS LCD Programme commits to attending diabetes review / monitoring appointments when offered, regardless of whether remission has been achieved
- Ongoing review and monitoring should be offered in line with usual care for people with Type 2 Diabetes

Coding of Remission

- The GP practice is requested to check HbA1c at 6 months and at 12 months after start of the programme
- In line with the definition put forward for the NHS LCD Programme pilots, the earliest point at which remission may be identified is therefore at 12 months
- **If remission is achieved, this should be coded as 'Type 2 Diabetes in remission'** (703138006)
- This code does not remove patients from the Diabetes Register - thus facilitating ongoing review and monitoring for complications of diabetes, as well as enabling QOF recognition to continue
- Please DO NOT use the code 'Diabetes Resolved' as it will remove the patient from the Diabetes Register

Coding the NHS LCD Programme

- Practices will be informed by the provider when a milestone relating to progress on the programme has been reached
- Correspondence from providers will explain which codes to use
- Note that the ‘completion’ code relates to the TDR phase of the programme rather than the entire programme length

Event	SNOMED code	SNOMED code description
Invitation	1239631000000109	Total diet replacement programme invitation
Referral	1239571000000105	Referral to total diet replacement programme
Declined	1239581000000107	Total diet replacement programme declined
Commenced	1239591000000109	Total diet replacement programme commenced
Not commenced	1239621000000107	Did not commence total diet replacement programme
Completed	1239601000000103	Total diet replacement programme completed (relates to 12 week TDR phase)
Not completed	1239611000000101	Did not complete total diet replacement programme
Contraindicated	1239541000000104	Total diet replacement programme contraindicated
Remission achieved	703138006	Type 2 Diabetes in remission

Offering the NHS LCD Programme to patients

- Pointers for enhancing the offer of a referral:
    - Provided it is clinically appropriate, please frame the offer of referral positively as something in which you expect the patient will be interested. Try not to assume the programme won't be acceptable to a patient
    - Early in the discussion about the programme, make clear that it is free-of-charge and that there is also no cost to the patient for the TDR products
    - If the programme is being delivered face-to-face, explain that it is delivered locally
    - Even if the delivery model uses groups, use the terms 'programme' or 'service' rather than 'group' or 'club'
    - Make clear that there is ongoing support available for a full year
    - Most participants report that hunger is not a major problem after the first week
    - Many people also feel younger with the rapid weight loss and this is self-motivating
    - Consider motivational interviewing to help overcome perceived barriers and support readiness to change

- An example script demonstrating discussion of referral to the NHS LCD Programme has been developed by the Nuffield Department of Primary Care Health Sciences at the University of Oxford. This is available on FutureNHS

Testimonials after an LCD TDR programme

Starting the diet

‘The first week or so I was probably feeling hungry but after that, absolutely fine. I did think, how am I going to manage on three drinks a day, but absolutely fine.’ (Man, aged 69 years, diabetes duration 3.5 years)

‘I was so surprised, compared to what I was eating to what I have been eating over the last weeks, I really would have thought that I would have been hungry from the moment I opened my eyes to the moment I closed my eyes, but I wasn’t.’ (Woman, aged 42 years, diabetes duration 1 year)

Regimen and structure

‘What I found with the diet is that the regimen suits me. I like to know what I’m going to have to eat. If I get choice, if I get here’s a shelf full of food go and choose something and potentially I can choose the wrong foods, so if I plan and know what it is that I’m going to eat then I can do it quite easily.’ (Man, aged 49 years, diabetes duration 9.5 years)

Physical wellbeing

‘It was fairly hard to start with but it got easier as the weeks went on and then when I started getting a bit fitter and I could walk further and stand up and sit down and dig the garden it’s great now. I feel great.’ (Man, aged 44 years, diabetes duration 2.5 years)

Psychological wellbeing

‘I think as my weight’s gone off I think my mood’s improved quite a bit. I feel quite, I think because I’m enjoying doing the diet and the research project and I’m looking forward to what’s going to happen in the future I think, I don’t know, I just feel more lighter.’ (Woman, aged 35 years, diabetes duration 1.5 years)

Common adverse effects incl. constipation

The most common adverse effects experienced during TDR in the DiRECT trial were constipation (46.8%), sensitivity to cold (41.0%), headache (38.1%), dizziness (35.3%) and fatigue (32.4%), as shown on the right

The Provider is responsible for supplying a starter pack of fibre supplements to participants, as well as the ongoing supply of fibre supplements during the programme

Unless there is a clinical reason why this would be inappropriate, participants should be recommended to commence fibre supplementation at the same time as initiating TDR, to reduce likelihood of constipation

Table S9: Adverse effects identified a priori as relevant to the intervention treatment, experienced by intervention group participants during year one at study visits in each phase of the weight management programme. The usual-care control group was seen only at baseline and 12 months.

	TDR phase (12-20 weeks)				FR phase (4-6 weeks)				WLM phase (26-36 weeks)			
	Total (n=139)	Mild	Moderate	Severe	Total (n=124)	Mild	Moderate	Severe	Total (n=94)	Mild	Moderate	Severe
Constipation	65 (46·8)	30 (21·6)	24 (17·3)	11 (7·9)	18 (14·5)	14 (11·3)	4 (3·2)	0 (0·0)	6 (6·4)	2 (2·1)	2 (2·1)	2 (2·1)
Sensitivity to cold	57 (41·0)	37 (26·6)	12 (8·6)	8 (5·8)	30 (24·2)	19 (15·3)	6 (4·8)	5 (4·0)	13 (13·8)	7 (7·4)	2 (2·1)	4 (4·3)
Headache	53 (38·1)	31 (22·3)	13 (9·4)	9 (6·5)	15 (12·1)	10 (8·1)	3 (2·4%)	2 (1·6)	8 (8·5)	5 (5·3)	2 (2·1)	1 (1·1)
Dizziness	49 (35·3)	40 (28·8)	7 (5·0)	2 (1·4)	11 (8·9)	3 (2·4)	6 (4·8)	2 (1·6)	7 (7·4)	4 (4·3)	3 (3·2)	0 (0·0)
Fatigue	45 (32·4)	24 (17·3)	11 (7·9)	10 (7·2)	18 (14·5)	10 (8·1)	3 (2·4)	5 (4·0)	8 (8·5)	2 (2·1)	0 (0·0)	6 (6·4)
Mood change	35 (25·2)	16 (11·5)	12 (8·6)	7 (5·0)	10 (8·1)	4 (3·2)	4 (3·2)	2 (1·6)	4 (4·3)	1 (1·1)	2 (2·1)	1 (1·1)
Nausea	25 (18·0)	15 (10·8)	4 (2·9)	6 (4·3)	3 (2·4)	3 (2·4)	0 (0·0)	0 (0·0)	1 (1·1)	1 (1·1)	0 (0·0)	0 (0·0)
Diarrhoea	23 (16·5)	11 (7·9)	10 (7·2)	2 (1·4)	5 (4·0)	4 (3·2)	1 (0·8)	0 (0·0)	1 (1·1)	1 (1·1)	0 (0·0)	0 (0·0)
Indigestion	20 (14·4)	15 (10·8)	3 (2·2)	2 (1·4)	4 (3·2)	2 (1·6)	2 (1·6)	0 (0·0)	1 (1·1)	1 (1·1)	0 (0·0)	0 (0·0)
Hair Loss	19 (13·7)	10 (7·2)	7 (5·0)	2 (1·4)	13 (10·5)	3 (2·4)	6 (4·8)	4 (3·2)	8 (8·5)	4 (4·3)	3 (3·2)	1 (1·1)

Data reported as N(%)

Adverse effects / events process

- Patients should be advised to contact the Provider directly if experiencing an adverse effect or concurrent event which is not considered an emergency
- To support this process, the Provider has a Medical Director with responsibility for:
    - Responding appropriately to adverse events;
    - Responding and giving advice about concurrent events;
    - Appropriately recording all adverse events and feeding back to the GP practice and NHS England / Improvement
- The Provider is expected to triage and respond appropriately to concurrent or adverse effects – this may include giving advice, signposting the patient to the GP practice for assessment / medication adjustment or directing the patient to urgent / emergency care services if an urgent medical need is identified
- **If a patient contacts the GP practice directly and is acutely unwell, it would clearly not be appropriate to redirect the patient to the Provider**
    - The Provider should be informed, by either the patient or the GP practice, at an appropriate time once urgent action has been taken and they will advise regarding next steps on the LCD Programme
    - e.g. if a patient complains of abdominal pain and has a clinical presentation in keeping with acute cholecystitis, the patient should be admitted to hospital without delay and should not be redirected to the Provider

Responsibilities – GP practice / LCD Provider

Referring GP Practice

Identify eligible patients and offer referral as appropriate

Provide information on concept of remission of Type 2 Diabetes, the LCD service and potential risks and benefits to obtain informed consent

Discuss medication changes to take place on first day of TDR and provide written confirmation of these change to the patient and Provider

Respond to any clinical need to further adjust medications according to capillary blood glucose and blood pressure monitoring by the Provider

Respond to adverse events if patient contacts practice directly with an urgent clinical need or is directed to the GP practice by the Provider

Arrange review of patient at 6 months and 12 months after starting LCD programme with repeat HbA1c – with further medication adjustment as necessary

LCD Service Provider

Attempt contact with patients referred within 5 working days to provide further information about the LCD service and book Individual Assessment

Confirm medication changes with patient in line with written instructions from referrer

Perform / arrange for monitoring of capillary blood glucose and blood pressure

Identify where capillary blood glucose and blood pressure fall outside of specified parameters and communicate appropriately with GP practice for further action

Act as initial contact for patients experiencing a concurrent or adverse event which is not considered an emergency

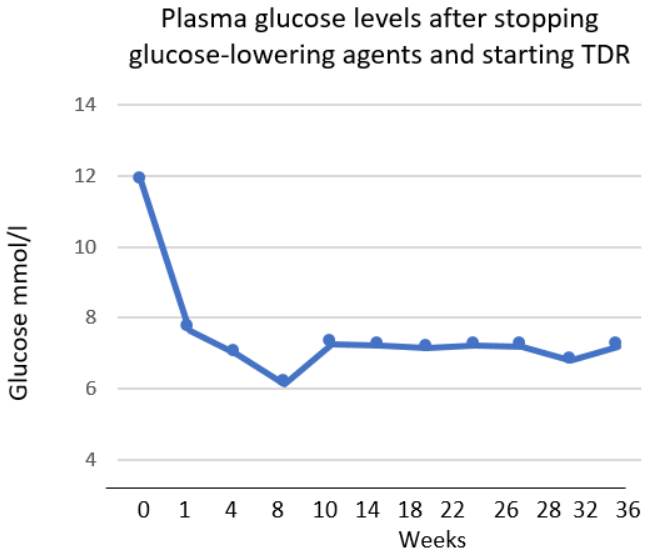
Appropriately triage and respond to adverse events – including signposting the patient to the GP practice or to other services

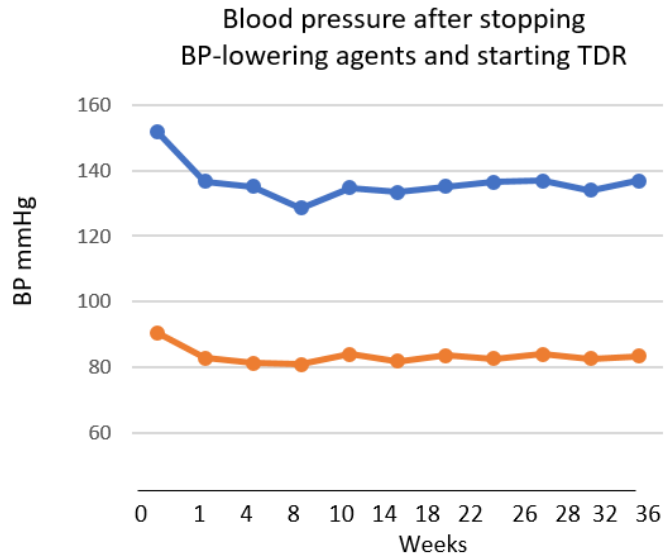
Provide a starter pack of fibre supplements and ongoing supply

Optimise uptake and retention on the programme

Blood glucose and BP changes on TDR

- As clinicians, we are generally more accustomed to starting medication than stopping medication
- It is recognised that instructing patients to stop glucose-lowering agents and BP-lowering agents on the first day of TDR may seem unusual to practitioners less familiar with the intervention
- The graphs on the right demonstrate findings from the Counterbalance study (which informed the DiRECT trial)
- There is a marked reduction in plasma glucose levels within a week on TDR, despite stopping all glucose-lowering agents
- Similarly, albeit less marked, there is a reduction in blood pressure levels within a week on TDR, despite stopping all BP-lowering agents





Approach to blood glucose and blood pressure

- Despite stopping all glucose-lowering agents at the outset, there were no hyperglycaemia-related adverse events in DiRECT in the intervention group
- In relation to cardiovascular events, the DiRECT trial analysis at two years noted that ‘serious adverse events included several vascular events in the control group (two cerebrovascular accidents, one toe amputation, one aortic aneurysm rupture, and one sudden death), compared with one non-fatal myocardial infarction in the intervention group in a participant who had not attended for review at either 12 months or 24 months’
- The approach to managing agents affecting blood glucose and blood pressure in the NHS LCD Programme is based on the approach used in DiRECT. However, it has been modified to reflect learning and adapted to a ‘real-world’ setting, with a more conservative approach to medication adjustment
- Though DiRECT stopped all BP-lowering medication on the first day of TDR, referrers to the NHS LCD Programme are advised to only adjust one BP-lowering medication initially. This is based on data from the trial for medication re-starts as well as evidence for more marked reductions in blood glucose than for blood pressure with TDR (as seen on the previous slide)
- Hypoglycaemic events should not occur during TDR as the patient MUST stop any drugs prone to causing hypoglycaemia before starting TDR – and will not be able to commence TDR unless this is confirmed
- **At referral, agreed medication changes must be provided in writing to the patient (SMS / email / printed) and the Provider (on referral form)**
- The medication adjustments recommendations outlined in this slide pack have been formulated by an Expert Advisory Group including the lead investigators of the DiRECT and DROPLET trials, consultant diabetologists and primary care clinicians. **The recommendations are designed to be safe, evidence-based and pragmatic. They do not replace clinical judgment and constitute guidance only. Clinical responsibility remains with the referring GP practice**

Monitoring of blood glucose and BP

- A key safety mechanism in the NHS LCD Programme is the regular monitoring of participants' blood glucose and blood pressure (in people prescribed agents affecting blood pressure at time of referral) to detect:
    - clinically significant hyperglycaemia
    - clinically significant high or low blood pressure
- If the programme is delivered remotely, participants will be supplied with equipment and training to undertake self-monitoring by the LCD Service Provider, with participants communicating readings directly to the Provider
- If the programme is delivered face-to-face, the Provider may perform monitoring directly or may make arrangements for self-monitoring
- Capillary blood glucose and blood pressure readings will therefore be received and interpreted by the Provider. Any readings requiring action, including adjustment of medications, will be communicated to the GP practice with appropriate urgency (see next slide)
- When on TDR (the 12-week TDR phase or 4-week 'rescue package'), capillary blood glucose and blood pressure will be checked at least weekly in weeks 1-4 and at least every 2 weeks in weeks 5-12
- When not on TDR, capillary blood glucose and blood pressure will be checked at least monthly
- **At 6 months and at 12 months after starting the programme, the GP practice should review the patient with repeat HbA1c**

Thresholds for communication / action

The provider will monitor capillary blood glucose readings and will communicate with the GP practice as follows:

- Under 15 mmol/l – no additional action required, continue intervention;
- Between 15.0 - 19.9 mmol/l over 2 Sessions – the Provider must contact the Service User's GP practice;
- 20.0 mmol/l or higher – there must be same-day contact with the Service User's GP practice team (the Provider must contact the GP practice directly and the Service User must also be advised to contact their GP practice same-day)

The provider will monitor BP in people prescribed agents affecting BP at time of referral and will communicate with the GP practice as follows:

- 89/59 mmHg or lower (systolic and/or diastolic) or postural symptoms – the Provider must contact the Service User's GP practice team. If symptoms are interfering with daily activities, same-day contact with the GP practice must be made (the Provider must contact the GP practice directly and the Service User must also be advised to contact their GP practice same-day);
- 90/60 to 159/99 mmHg – no additional action required, continue intervention;
- 160/100 to 179/119 mmHg (systolic and/or diastolic) over two sessions – Provider must contact the Service User's GP practice;
- 180/120 mmHg or higher (systolic and/or diastolic) – there must be same-day contact with the Service User's GP practice (the Provider should contact the GP practice directly and the Service User must also be advised to contact their GP practice same-day);
- For avoidance of doubt, if a blood pressure reading fits into two of the categories described above (such as 181/118 mmHg), action should be taken in line with the category prompting the most rapid response (in this case, same-day contact with the GP practice)

Medication adjustments when starting TDR – glucose-lowering agents

Discussion at time of referral – stopping glucose-lowering agents on the first day of TDR – recommendations

- People on 1-2 glucose-lowering agents should stop these agents on the first day of TDR [it is likely that most patients will be in this group]
- People on ≥ 3 agents should stay on metformin only (or, if not taking metformin as it is contraindicated / not tolerated, stay on an oral agent which is safe with TDR, e.g. DPP4 inhibitor or pioglitazone) and stop the remaining glucose-lowering agents on the first day of TDR

- The medication changes (including the absence of any changes) must be specified in writing to the patient and LCD provider at time of referral
- Counsel the patient about the osmotic symptoms of diabetes and when and how to seek appropriate support

- (Sulfonylureas, meglitinides, SGLT2 inhibitors are not safe with TDR and MUST be stopped on the first day of TDR)
- (GLP-1 analogues will confound weight loss outcomes and therefore should be stopped on the first day of TDR)

Which glucose-lowering agents are safe with TDR?

Class of medication	Examples of drugs	Is this safe with TDR?
Biguanides	Metformin	Yes – safe
Sulfonylureas	Gliclazide, Glibenclamide, Glimepiride	No – risk of hypoglycaemia
Meglitinides	Repaglinide, Nateglinide	No – risk of hypoglycaemia
Thiazolidinediones	Piogliazone	Yes - safe
DPP4 inhibitors (-gliptins)	Linagliptin, Alogliptin, Sitagliptin, Saxagliptin, Vildagliptin	Yes - safe
SGLT2 inhibitors (-flozins)	Dapagliflozin, Canagliflozin, Empagliflozin, Ertugliflozin	No – risk of ketoacidosis
GLP-1 analogues (-tides)	Exenatide, Dulaglitide, Liraglutide, Lixisenatide, Semaglutide	Yes - safe
Alpha-glucosidase inhibitors	Acarbose	Yes – safe
(insulin is not included here as people treated with insulin are not eligible for the NHS LCD Programme pilots)		

Examples – 1 or 2 glucose-lowering agents

1 glucose-lowering agent at time of referral – stop the agent on first day of TDR

- patient is on metformin only at time of referral – 1 agent
    - stop the agent (metformin) on the first day of TDR. This will be the case for any instances of monotherapy for glycaemia

2 glucose-lowering agents at time of referral – stop both agents on first day of TDR

- patient is on metformin and SGLT2 inhibitor at time of referral – 2 agents
    - stop both these agents (metformin and SGLT2 inhibitor) on the first day of TDR. This will be the case for any instances of dual therapy for glycaemia (Also note that the SGLT2 inhibitor is not safe with TDR).
- patient is on metformin and sulfonylurea at time of referral – 2 agents
    - stop both these agents (metformin and sulfonylurea) on the first day of TDR. This will be the case for any instances of dual therapy for glycaemia

Examples – ≥ 3 glucose-lowering agents

≥ 3 glucose-lowering agents at time of referral – stay on metformin (or, if metformin contraindicated / not tolerated, another oral agent which is safe with TDR, e.g. DPP4-i or pioglitazone) and stop the remaining agents on first day of TDR

- patient is on metformin, sulfonylurea and DPP4 inhibitor at time of referral – 3 agents
    - stop the sulfonylurea and DPP4 inhibitor on the first day of TDR but stay on metformin
- patient is on sulfonylurea, SGLT2 inhibitor and GLP-1 analogue (metformin not tolerated) at time of referral – 3 agents [may not be licensed]
    - stop all three of these agents on the first day of TDR
- patient is on sulfonylurea, SGLT2 inhibitor, and DPP4 inhibitor (metformin not tolerated) at time of referral – 3 agents [may not be licensed]
    - stop the sulfonylurea and SGLT2 inhibitor on the first day on TDR but stay on DPP4 inhibitor
- patient is on DPP4 inhibitor, pioglitazone and SGLT2 inhibitor (metformin not tolerated) at time of referral – 3 agents [may not be licensed]
    - stop the SGLT2 inhibitor and one of the other glucose-lowering agents (DPP4 inhibitor and pioglitazone) on the first day of TDR – i.e. only stay on either DPP4 inhibitor or pioglitazone (not both)
- patient is on metformin, pioglitazone, SGLT2 inhibitor and GLP-1 analogue at time of referral – 4 agents [may not be licensed]
    - stop pioglitazone, SGLT2 inhibitor and GLP1-analogue on the first day of TDR but stay on metformin

Rationale for approach at referral – glucose-lowering agents

- It is recommended that people taking 1-2 glucose-lowering agents stop these at the outset to give them the opportunity to achieve remission – the definition of which includes the requirement to have stopped all glucose-lowering agents
- The rationale for a different approach for people on ≥ 3 glucose-lowering agents (recommended to stay on metformin or one other oral drug which does not pose harm on TDR) is based on data from DiRECT. This showed a strong inverse relationship between the likelihood of achievement / maintenance of remission at 2 years and the number of agents for diabetes that the patient was taking at the outset. Though numbers of people taking ≥ 3 glucose-lowering agents were small, none maintained remission at 2 years
- There are a number of different factors which affect the number of glucose-lowering agents that a patient is taking – duration of diabetes, glycaemic control, frequency of review, practice / local processes etc – however, given the data from DiRECT, it is considered reasonable for patients taking ≥ 3 glucose-lowering agents to stay on metformin (or one other oral drug which does not pose harm on TDR) as it appears that they are unlikely to achieve remission and, in DiRECT, all such patients had restarted at least one glucose-lowering agent by 24 months
- However, if a patient on ≥ 3 glucose-lowering agents is keen to stop all these agents on the 1st day of TDR, this is still acceptable. The patient should be made aware that glucose-lowering agents may need to be restarted during the course of the programme

Restarting glucose-lowering agents

- The clinical need to restart medication to control glycaemia may arise during the LCD programme
- This may be flagged by the Provider from monitoring of capillary blood glucose levels or identified by the GP practice following review of HbA1c at 6 months
- Metformin is 1st line and is also safe in TDR (check other contraindications / cautions)
- Pioglitazone or DPP4 inhibitors are also safe in TDR (check other contraindications / cautions) and may be started if clinically appropriate
- GLP-1 analogues are safe in TDR but high cost and may confound weight loss outcomes - may be restarted if clinically appropriate, in line with NICE guidance Consider triple therapy by switching one drug for a GLP 1 mimetic to reflect that people might be taking an SGLT2 inhibitor, in line with Nice guidance
- Sulfonylureas, meglitinides or SGLT2 inhibitors
    - These agents MUST NOT be used during TDR for safety reasons
    - If the patient is on TDR and there is a clinical need to control glycaemia and only these agents are clinically appropriate, the patient MUST be told to stop TDR with immediate effect and the provider MUST be informed straight away if any of these agents are restarted
    - If the patient has stopped TDR and there is a clinical need to control glycaemia and only these agents are clinically appropriate, the provider MUST still be informed if any of these agents are restarted
    - Restarting these agents while the patient is on the LCD programme will also preclude ‘rescue TDR’ initiation – consider alternative agents if possible
- If insulin initiation is deemed clinically necessary at any stage, the patient MUST be told to cease the LCD programme with immediate effect and the Provider MUST be informed straight away

Supporting information – glucose-lowering agents

- The class of sulfonylureas includes gliclazide, glibenclamide, glimepiride, glipizide, tolbutamide – for safety, these MUST not be used with TDR due to high risk of causing hypoglycaemia (stimulate insulin release independent of blood glucose levels). Even if the TDR phase has been completed, consider alternative agents if possible as restarting sulfonylureas while the patient is on the LCD programme will preclude 'rescue TDR' initiation
- The class of meglitinides includes repaglinide, nateglinide – for safety, these MUST not be used with TDR due to high risk of causing hypoglycaemia (stimulate insulin release independent of blood glucose levels). Even if the TDR phase has been completed, consider alternative agents if possible as restarting meglitinides while the patient is on the LCD programme will preclude 'rescue TDR' initiation
- The class of SGLT2 inhibitors includes dapagliflozin, canagliflozin, empagliflozin, ertugliflozin – for safety, these MUST not be used with TDR due to risk of ketoacidosis (the TDR diet is ketogenic). Even if the TDR phase has been completed, consider alternative agents if possible as restarting SGLT2 inhibitors while the patient is on the LCD programme will preclude 'rescue TDR' initiation

- Metformin – safe with TDR but check other contraindications / cautions - 1st line agent to restart if clinically appropriate and control of glycaemia required
- Pioglitazone – safe with TDR but check other contraindications / cautions – can be restarted if necessary and clinically appropriate to further control glycaemia although metformin is 1st line
- The class of DPP4 inhibitors includes alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin – safe with TDR but check other contraindications / cautions - can be restarted if necessary and clinically appropriate to control glycaemia although metformin is 1st line
- The class of GLP-1 analogues includes exenatide, dulaglitide, liraglutide, lixisenatide, semaglutide – these are safe with TDR but are high cost and may confound weight loss outcomes - can be restarted if necessary and clinically appropriate, in line with NICE guidance. Consider triple therapy by switching one drug for a GLP 1 mimetic to reflect that people might be taking an SGLT2 inhibitor, in line with Nice guidance

Medication adjustments when starting TDR – BP-lowering agents

Note that BP-lowering agents include medicines used for other indications (e.g. tamsulosin for benign prostatic hypertrophy, furosemide for oedema) as well as medicines used specifically for managing blood pressure

Discussion at time of referral – adjusting BP-lowering agents on the first day of TDR – recommendations:

- If blood pressure is considered uncontrolled at time of referral (systolic ≥ 140mmHg or diastolic ≥ 90mmHg), make no changes to BP-lowering agents
- If blood pressure is considered controlled at time of referral (both systolic < 140mmHg and diastolic < 90mmHg), one BP-lowering agent should be adjusted on the first day of TDR
- If reviewing the patient remotely, it is reasonable to use self-reported blood pressure. If not available, the last clinic-recorded blood pressure may be used, provided there have been no intervening changes to lifestyle or medications affecting blood pressure, there is no history of white-coat hypertension, and there is no concern that blood pressure may have changed significantly since last measured
- The medication changes (including the absence of changes) must be specified in writing to the patient and LCD provider
- Counsel the patient about symptoms of postural hypotension and advise them of when and how to seek appropriate support

Medication adjustments when starting TDR – BP-lowering agents

- It is recognised that people may be taking a variety of combinations of medications, at different doses, which affect blood pressure. This guidance makes various assumptions which will not reflect the management of every patient
- It is therefore imperative that clinical judgement is used
- An agent may be used in one patient solely for managing blood pressure while, in another patient, it may also be used for another indication, e.g. ACE-inhibitors in heart failure with reduced ejection fraction (HFREF)
- **Agents being used specifically and solely for managing blood pressure, in a particular patient, are the priority for adjustment**

Selecting the BP-lowering agent for adjustment

- Identify the agents used in the patient solely for managing blood pressure (i.e. not also being used for nephropathy, angina, heart failure, BPH, migraines etc) - this must be checked on the records and confirmed with the patient
- Stop the agent would have been added last according to current NICE guidance [at present, this is NICE guideline NG136 (2019): Hypertension in adults: diagnosis and management] - unless other clinical factors affect decision making
- If not being used for other indications, this would be (in order of stopping first):
    - Spironolactone or alpha-blocker or beta-blocker
    - Thiazide diuretic (or calcium-channel blocker)
    - Calcium-channel blocker (or thiazide diuretic)
    - ACE-inhibitor or Angiotensin receptor blocker
- If the patient is taking agents which affect blood pressure but all are being used for other indications (none are being used solely to manage blood pressure):
    - use clinical judgement and shared decision making and take into account the blood pressure reading
    - cautiously reduce the dose of this agent rather than stopping it
    - consider arranging early review to monitor clinical response, in relation to the specific indication for the agent
    - in some circumstances, it may be reasonable not to adjust these agents initially but to carefully monitor and respond accordingly

Examples – at least one agent used solely for BP

Blood pressure is considered controlled at time of referral – (both systolic < 140mmHg and diastolic < 90mmHg)

- patient is taking ramipril 10mg (for BP solely – no other indications) at time of referral
    - stop the ramipril 10mg on the first day of TDR
- patient is taking ramipril 10mg (for BP solely) and amlodipine 10mg (for BP solely) at time of referral
    - stop the amlodipine 10mg on the first day of TDR
    - the amlodipine would be added last according to NICE guidance for hypertension and therefore is stopped first
- patient is taking ramipril 10mg (prev MI), amlodipine 10mg (for BP solely), indapamide mr 1.5mg (for BP solely), bisoprolol 10mg (prev MI) at time of referral
    - stop indapamide mr 1.5mg (or, alternatively, adjust the amlodipine 10mg)
    - although bisoprolol would be added last according to NICE guidance for hypertension, it is used here for another indication and therefore should not be adjusted at this time
    - excluding bisoprolol, the indapamide would have been added last according to current NICE guidance for hypertension and therefore is stopped first

Examples – no agents used solely for BP

Blood pressure is considered controlled at time of referral – (both systolic < 140mmHg and diastolic < 90mmHg)

- patient is taking ramipril 10mg (for nephropathy) at time of referral
    - reduce ramipril dose to 5mg rather than stopping
- patient is taking propranolol 40mg bd (for migraine prophylaxis), doxazosin 2mg (for BPH) at time of referral
    - discuss options, balancing potential impact on migraine frequency / LUTs symptoms against risks of hypotension with TDR on these agents
    - given the low doses in this example, may be reasonable not to make any changes to these agents at this time – if so, careful monitoring required
    - if medication adjusted, advisable to arrange review of migraines / LUTs symptoms at clinically appropriate interval
- patient is taking ramipril 10mg (HFREF), bisoprolol 10mg (HFREF), furosemide 60mg (HFREF) at time of referral
    - needs a cautious approach – inadvisable to suddenly stop an agent in this example unless strong clinical rationale
    - carefully reduce dose of one agent – use clinical judgement and shared decision making
    - early clinical review, including assessment of fluid status (particularly if adjusting furosemide), should be arranged

Subsequent adjustment of agents for BP

Blood pressure is too low

- If postural symptoms arise or blood pressure is reported by the Provider to be low (systolic < 90 mmHg and/or diastolic < 60mmHg), follow the same process as previously outlined in adjusting BP-lowering agents
- Agents being used specifically and solely for managing BP in a particular patient, are the priority for adjustment

Blood pressure is too high

- If blood pressure (monitored by the Provider) rises to a threshold where intensification of antihypertensive treatment is clinically indicated, use clinical judgement in restarting or uptitrating doses of agents
- Assess whether any previously-adjusted agents used for other indications (rather than solely for managing blood pressure) should be restarted / up-titrated first
- Follow NICE guidance in restarting antihypertensive therapy (unless other clinical factors affect decision making)

Medications needing adjustment – weight / dietary changes

- Some medications may need to be adjusted due to changes in body weight or dietary intake
- Some of these medicines are likely to be prescribed by the GP practice while others may be prescribed or administered by other services. If prescribed or administered by other services, these may not appear on the patient record on the GP IT system
- It is therefore important to ask the patient if they are receiving medication or treatment in other settings
- Ask yourself ‘‘if someone lost weight or had a major dietary change, is the dose of this medicine likely to need adjustment?’
- If in doubt, discuss with a pharmacist colleague
- **It is the responsibility of the referrer to make sure that processes are in place for any applicable medications to be adjusted**
- Only refer the patient if safe, robust processes are in place to manage the adjustment of these medicines in line with dietary or weight changes. As a minimum, establish who will be responsible for obtaining weight readings (or other monitoring – e.g. INR for warfarin), the frequency, how this will be recorded, how the prescriber will be notified and how dose changes will be communicated with the patient
- If involving other services, such as specialist clinics, prior discussion with such services must take place to establish feasibility, responsibility and agreement for appropriately frequent patient review and dose adjustment
- **If this cannot be done safely then the patient should not be referred to the LCD programme**

Medications needing adjustment – weight / dietary changes

- It is not possible to provide an exhaustive list of all medications which may need adjustment due to weight / dietary changes
- Commonly used oral medicines which may require adjustment include:
    - Warfarin
    - Non-vitamin K antagonist oral anticoagulants (NOACs)
    - Digoxin
    - Phenytoin
    - Ciclosporin
    - Antifungals – voriconazole
    - Long-term antibiotic therapy (e.g. isoniazid)
- Many medicines administered parentally may require dose adjustment by weight. These include:
    - Low molecular weight heparin
    - Infliximab (and other biologics)
    - Long-term antibiotic therapy (e.g. macrolides, aminoglycosides, fluoroquinolones, beta-lactams)

Pre-referral checklist

- ❑ Checked eligibility and made sure no exclusions apply
- ❑ Checked list of medications currently prescribed / taken (including those prescribed by other healthcare services such as hospitals) and identified:
    - ❑ Medicines for glycaemia
    - ❑ Medicines which affect blood pressure (including those which may not being used specifically to treat blood pressure, e.g. furosemide or tamsulosin)
    - ❑ Medicines which may need to be adjusted due to changes in body weight or diet - ask yourself, 'if someone lost weight or had a major dietary change, is the dose of this medicine likely to need adjustment?'
        - if in doubt, discuss with a pharmacist colleague
        - only refer if safe, robust processes are in place to manage adjustment of these medicines and appropriate review in line with dietary / weight changes
- ❑ Agreed medication adjustments with the patient (for 1st day of TDR) – **must be specified in writing to the patient and LCD provider (incl. if no changes are needed)**
        - recommended adjustments for glucose-lowering agents and agents for blood pressure are described in this slide pack
        - use your clinical judgement – if in doubt, discuss with the LCD service provider
        - patients will not be able to start TDR unless the provider confirms that they are stopping / not taking sulfonylureas, meglitinides or SGLT2-inhibitors
- ❑ Confirmed with the patient that they will continue attending diabetes review appointments / monitoring at their GP practice, regardless of whether remission is achieved
- ❑ Confirmation that patient will notify the GP practice of any unexpected or concerning symptoms which are considered urgent
- ❑ Confirmed with the patient that they will notify the GP practice if they disengage or drop out before the end of the intervention (medication may need to be restarted)
- ❑ Counselled the patient appropriately and obtained valid, informed consent to refer